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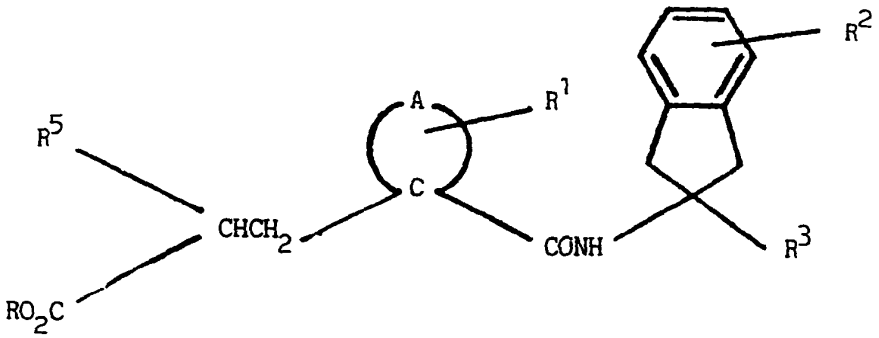

(I)

(57) Abstract

Compounds of formula (I), wherein A completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring; R is H, C_1-C_6 alkyl, benzyl or an alternative biolabile ester-forming group; R^1 is H or C_1-C_4 alkyl; R^2 is H, OH, C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or CF_3; R^3 is CH_2OH or CO_2R^4 where R^4 is as defined for R; and R^5 is defined to include a range of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and substituted alkyl groups including in particular methoxyethyl, S-lysylaminomethyl, N^2-acetyl-S-lysylaminomethyl and N^2-m thanesulphonyl-S-lysyl-aminomethyl, are atriopeptidase inhibitors of utility in the treatment of hypertension, heart failure, renal insufficiency and other disorders

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"Cycloalkyl-substituted glutaramide diuretic agents

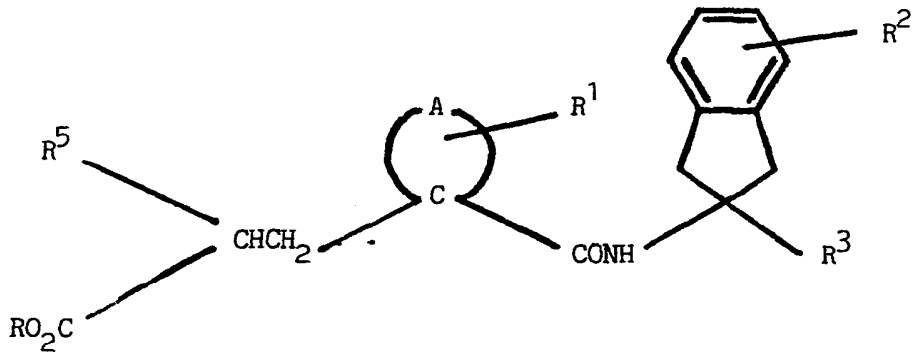
This invention relates to a series of cycloalkyl-substituted glutaramide derivatives which are diuretic agents having utility in a variety of therapeutic areas including the treatment of various cardiovascular disorders such as hypertension, heart failure and renal insufficiency.

According to the specification of our European patent applications EP-A-0274234 and EP-A-0343911 we describe and claim certain cycloalkyl-substituted glutaramide derivatives as diuretic agents. The present invention provides further related compounds having a 2,3-dihydroindene substituent.

The compounds are inhibitors of the zinc-dependent, neutral endopeptidase E.C.3.4.24.11. This enzyme is involved in the breakdown of several peptide hormones, including atrial natriuretic factor (ANF), which is secreted by the heart and which has potent vasodilatory, diuretic and natriuretic activity. Thus, the compounds of the invention, by inhibiting the neutral endopeptidase E.C.3.4.24.11, can potentiate the biological effects of ANF, and in particular the compounds are diuretic agents having utility in the treatment of a number of disorders, including hypertension, heart failure, angina, renal insufficiency, premenstrual syndrome, cyclical oedema, Menières disease, hyperaldosteronism (primary and secondary) pulmonary oedema, ascites, and hypercalciuria. In addition, because of their ability to potentiate the effects of ANF the compounds have utility in the treatment of glaucoma. As a further result of their ability to inhibit the neutral endopeptidase E.C.3.4.24.11

the compounds of the invention may have activity in other therapeutic areas including for example the treatment of asthma, inflammation, pain, epilepsy, affective disorders, dementia and geriatric confusion, obesity and gastrointestinal disorders (especially diarrhoea and irritable bowel syndrome), the modulation of gastric acid secretion and the treatment of hyperreninaemia and leukaemia.

The compounds of the present invention are of the formula:



(I)

wherein A completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring ;

R is H, C_1-C_6 alkyl, benzyl or an alternative biolabile ester-forming group;

R^1 is H or C_1-C_4 alkyl;

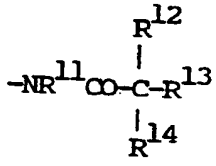
R^2 is H, OH, C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or CF_3;

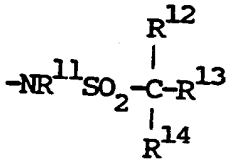
R^3 is CH_2OH or CO_2R^4 wherein R^4 is as previously defined for R;

and R^5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkenyl,

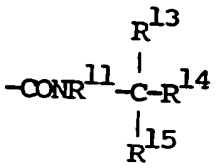
or R^5 is C_1-C_6 alkyl substituted by halo, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkoxy(C_1-C_6)alkoxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, aryl, aryloxy, heterocyclyl, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^{10}$, $-CONR^6R^7$ or R^6R^7N-(C_1-C_6)alkoxy;

or R^5 is C_1-C_6 alkyl substituted by a group of the formula:





or



wherein R^6 and R^7 are each independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, aryl, aryl(C_1-C_4)alkyl, C_2-C_6 alkoxyalkyl, or heterocyclyl; or the two groups R^6 and R^7 are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C_1-C_4)alkyl-piperazinyl group;

R^8 is H or C_1-C_4 alkyl;

R^9 is C_1-C_4 alkyl, CF_3, aryl, aryl(C_1-C_4)alkyl, aryl(C_1-C_4)alkoxy, heterocyclyl, C_1-C_4 alkoxy or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{10} is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, aryl or heterocyclyl;

R^{11} is H, C_1-C_6 alkyl, aryl or C_3-C_7 cycloalkyl;

R^{12} is $R^{11}CONR^{11}$-, $R^{11}SO_2NR^{11}$-, $R^{16}R^{17}N$-$(CH_2)_p$-, or $R^{11}O$-, wherein each R^{11} is as previously defined above;

R^{13} and R^{14} are each independently H or C_1-C_6 alkyl; or R^{13} is H and R^{14} is C_1-C_6 alkyl which is substituted by OH, C_1-C_4 alkoxy, SH, SCH_3, NH_2, aryl(C_1-C_6)alkyl-OCONH-, NH_2CO-, CO_2H, guanidino, aryl, or heterocyclyl; or the two groups R^{13} and R^{14} are joined together to form, with the carbon atom to which they are attached, a 5 or 6 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be

substituted by C_1-C_4 alkyl or fused to a further 5 or 6 membered saturated or unsaturated carbocyclic ring;

or R^{13} is H, and R^{12} and R^{14} are linked to form a 2-(N-COR^{11}-4-aminopyrrolidinyl) group;

R^{15} is $R^{16}R^{17}NCO$-, $R^{11}OCO$-, $R^{11}OCH_2$- or heterocyclyl, wherein R^{11} is as previously defined above;

R^{16} and R^{17} are each independently H or C_1-C_6 alkyl;

and p is 0 or an integer of from 1 to 6;

and pharmaceutically acceptable salts thereof and bioprecursors therefor.

In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms may be straight or branched-chain. The term aryl as used herein means an aromatic hydrocarbon group such as phenyl, naphthyl or biphenyl which may optionally be substituted with one or more OH, CN, CF_3, C_1-C_4 alkyl, C_1-C_4 alkoxy groups or halo atoms. Halo means fluoro, chloro, bromo or iodo.

The term heterocyclyl means a 5 or 6 membered nitrogen, oxygen or sulphur containing heterocyclic group which, unless otherwise stated, may be saturated or unsaturated and which may optionally include a further oxygen or one to three nitrogen atoms in the ring and which may optionally be benzofused or substituted with for example, one or more halo, C_1-C_4 alkyl, hydroxy, carbamoyl, benzyl, oxo, amino or mono or di-(C_1-C_4 alkyl)amino or (C_1-C_4 alkanoyl)amino groups. Particular examples of heterocycles include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, indolyl, isoindolinyl, quinolyl, quinoxalinyl, quinazolinyl and benzimidazolyl, each being optionally substituted as previously defined.

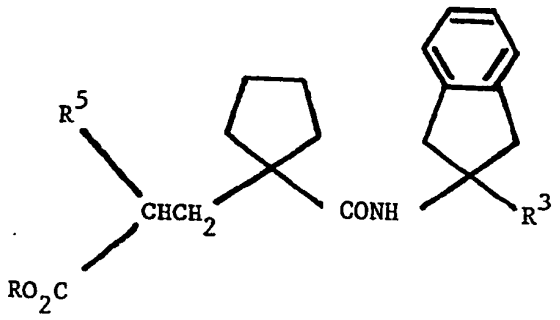
The compounds of formula (I) may contain several asymmetric centres and thus they can exist as enantiomers and diastereomers. The invention includes both mixtures and the separated individual isomers.

The pharmaceutically acceptable salts of the compounds of formula (I) containing an acidic centre are those formed with bases which form non-toxic salts. Examples include the alkali metal salts such as the sodium, potassium or calcium salts or salts with amines such as diethylamine. Compounds having a basic centre can also form acid addition salts with pharmaceutically acceptable acids. Examples include the hydrochloride hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, citrate, fumarate, gluconate, lactate,

maleate, succinate and tartrate salts.

The term bioprecursor in the above definition means a pharmaceutically acceptable biologically degradable derivative of the compound of formula (I) which, upon administration to an animal or human being, is converted in the body to produce a compound of the formula (I).

A preferred group of compounds of the formula (I) are those wherein A is $(CH_2)_4$ and R^1 and R^2 are H, i.e. compounds of the formula (II) below wherein R, R^3 and R^5 are as previously defined for formula (I):



(II)

Also preferred are those compounds of formulae (I) and (II) wherein R and R^4 (when R^3 is CO_2R^4) are both H (diacids) as well as biolabile mono and di-ester derivatives thereof wherein one or both of R and R^4 is a biolabile ester-forming group.

The term biolabile ester-forming group is well understood in the art as meaning a group which provides an ester which can be readily cleaved in the body to liberate the corresponding diacid of formula (I) wherein R and R^4 are both H. A number of such

ester groups are well known, for example in the penicillin area or in the case of the ACE-inhibitor antihypertensive agents.

In the case of the compounds of formulae (I) and (II) such biolabile pro-drug esters are particularly advantageous in providing compounds of the formula (I) suitable for oral administration. The suitability of any particular ester-forming group can be assessed by conventional animal or in vitro enzyme hydrolysis studies. Thus, desirably for optimum effect, the ester should only be hydrolysed after absorption; accordingly, the ester should be resistant to hydrolysis before absorption by digestive enzymes but should be readily hydrolysed by, for example, liver enzymes. In this way the active diacid is released into the bloodstream following oral absorption.

In addition to lower alkyl esters (particularly ethyl) and benzyl esters, suitable biolabile esters include alkanoyloxyalkyl esters, including alkyl, cycloalkyl and aryl substituted derivatives thereof, aryloxyalkyl esters, aroyloxyalkyl esters, arylalkyloxyalkyl esters, arylesters, aralkylesters, and haloalkyl esters wherein said alkanoyl groups have from 2 to 8 carbon atoms and said alkyl groups have from 1 to 8 carbon atoms and are branched or straight chain and said aryl groups are phenyl, naphthyl or indanyl optionally substituted with one or more C_1-C_4 alkyl or C_1-C_4 alkoxy groups or halo atoms.

Thus examples of R and R^4 when they are biolabile ester-forming groups other than ethyl and benzyl include: 1-(2,2-diethylbutyryloxy)ethyl, 2-ethylpropionyloxymethyl, 1-(2-ethylpropionyloxy)ethyl, 1-(2,4-dimethylbenzoyloxy)ethyl,

1-(benzoyloxy)benzyl, 1-(benzoyloxy)ethyl, 2-methyl-1-propionyloxypropyl, 2,4,6-trimethylbenzoyloxymethyl, 1-(2,4,6-trimethyl-benzyloxy)ethyl, pivaloyloxymethyl, phenethyl, phenpropyl, 2,2,2-trifluoroethyl, 1- or 2-naphthyl, 2,4-dimethylphenyl, 4-t-butyl-phenyl, 5-(4-methyl-1,3-dioxalynyl-2-onyl)methyl and 5-indanyl.

Compounds of the formulae (I) and (II) wherein R is benzyl or t-butyl and R^4 is ethyl are valuable intermediates for the preparation of the diacids wherein R and R^4 are both H.

In a further preferred group of compounds R^5 is methylene substituted by a group of the formula $-NHCOCR^{12}R^{13}R^{14}$, particularly where R^{12} is NH_2, $R^{11}CONH-$ or $R^{11}SO_2NH-$, R^{13} is H and R^{14} is $-(CH_2)_4NH_2$. Particularly preferred are such groups derived from S-lysine; thus especially preferred R^5 substitutents of this type include S-lysyl-aminomethyl, N^2-acetyl-S-lysylaminomethyl and N^2-methanesulphonyl-S-lysyl-aminomethyl.

In further groups of preferred compounds R^5 is C_1-C_6 alkyl, or C_1-C_6 alkyl substituted by C_1-C_6 alkoxy, particularly methoxyethyl; or R^5 is C_1-C_6 alkyl substituted by phenyl.

Particularly preferred individual compounds of the invention include:

2-{1-[2(S)-carboxy-3-(S-lysylamino)propyl]cyclopentyl-carbonylamino}-2,3-dihydroindene-2-carboxylic acid,

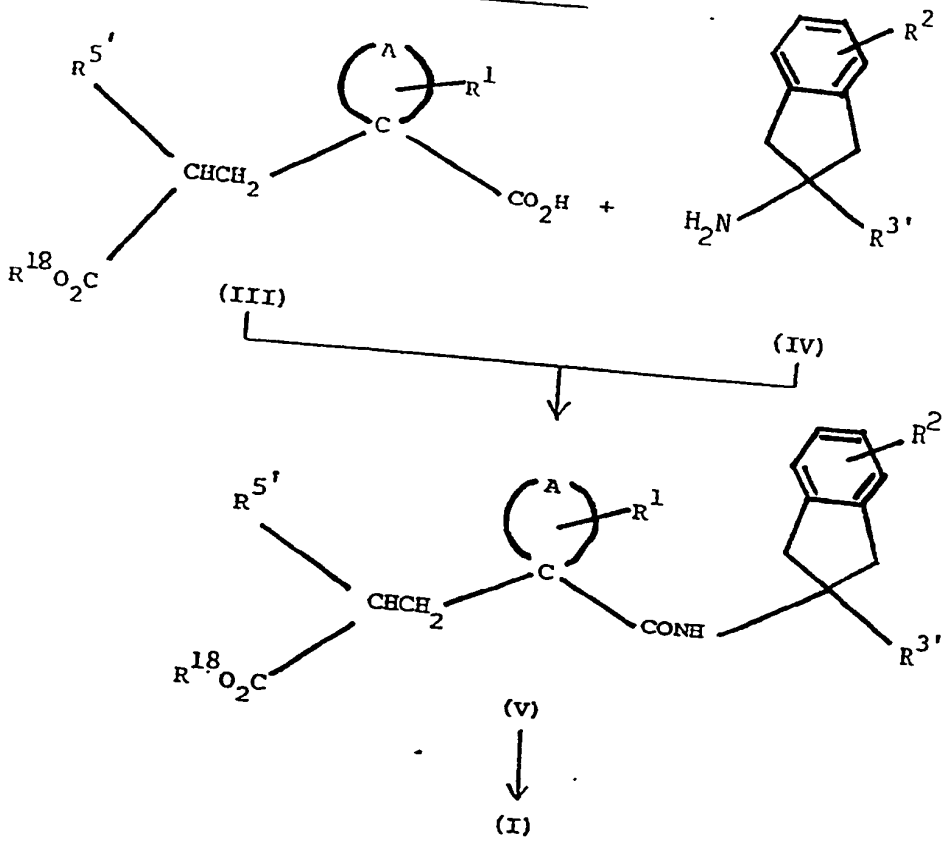
2-{1-[2(S)-carboxy-3-(N^2-methanesulphonyl-S-lysylamino)-propyl]cyclopentylcarbonylamino}-2,3-dihydroindene-2-carboxylic acid, and

2-{1-[2(S)-carboxy-3-(N^2-methanesulphonyl-S-lysylamino)-propyl]cyclopentylcarbonylamino}-2-hydroxymethyl-2,3-dihydroindene and biolabile ester derivatives thereof.

The compounds of formula (I) are prepared by a number of different processes. The basic procedure involves the synthesis of a partially protected cycloalkyl-substituted glutaric acid derivative which is coupled to an amine to give the desired glutaramide. The carboxylic acid group in the amine, if free, or any reactive groups in R^5, may require protection during the coupling step and such protecting groups are removed in the final stages of the process.

The synthetic route is illustrated in Scheme 1 wherein A, R^1 and R^2 are as previously defined, $R^{5'}$ is as defined for R^5 with any reactive group therein protected if necessary, R^{18} is as defined for R excluding H, or is a conventional carboxylic acid protecting group, and $R^{3'}$ is either CH_2OH or CO_2R^{19} wherein R^{19} is as previously defined for R^4 excluding H or is a conventional carboxylic acid protecting group:

Scheme 1



The reaction of the compounds of formula (III) and (IV) is achieved using conventional amide coupling techniques. Thus in one process the reaction is achieved with the reactants dissolved in an organic solvent, e.g. dichloromethane, using a diimide condensing agent, for example 1-ethyl-3-(dimethylaminopropyl)-carbodiimide, or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of 1-hydroxybenzotriazole and an organic base such as 4-methylmorpholine. The reaction is generally complete after a period of from 12 to 24 hours at room temperature and the product is then isolated by conventional procedures, i.e. by washing with water or filtration to remove the urea by-product and evaporation of the solvent. The product may be further purified by

crystallisation or chromatography, if necessary. The compounds of formula (V) include compounds of formula (I) wherein R and R^4 are C_1-C_6 alkyl or benzyl.

In some cases the coupled product, in protected form, may be subjected to conventional chemical transformation reactions to allow preparation of further compounds of formula (V). Thus for example compounds of formula (V) wherein $R^{5'}$ contains an ester group may be hydrolysed or hydrogenated to generate the carboxylic acid which may be further reacted, for example with an amine, to give amide derivatives.

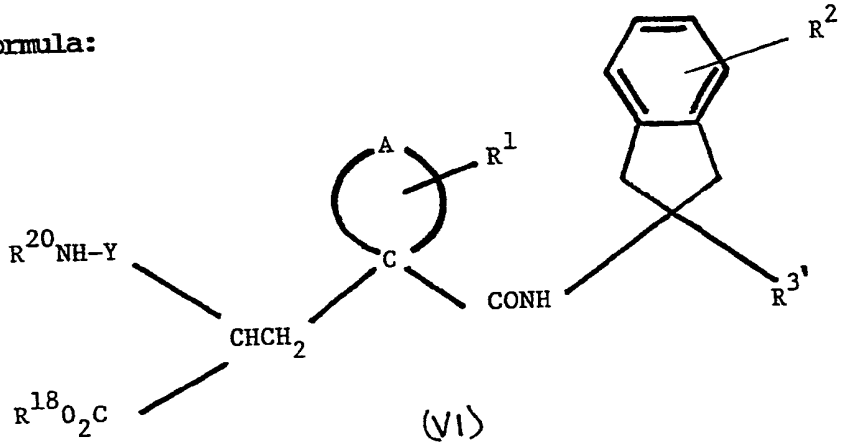
Similarly compounds wherein $R^{5'}$ contains a substituted or protected amino group (for example a benzylamino, dibenzylamino, benzyloxycarbonylamino or t-butyloxycarbonylamino group) may be converted to the free amines by hydrogenation or protonolysis as appropriate. The amines produced may be further reacted, thus for example reaction with a sulphonyl halide yields the corresponding sulphonamides, acylation with an acid chloride or anhydride yields the corresponding amides, reaction with an isocyanate yields urea derivatives and reaction with a chloroformate yields the carbamate products respectively. All these transformations are entirely conventional and appropriate conditions and reagents for their performance will be well known to those skilled in the art as will other variations and possibilities.

The diesters of formula (V) wherein $R^{3'}$ is CO_2R^{19} may be further reacted to give the monoester of diacid derivatives of formula (I) wherein one or both of R and R^4 are H. The conditions used will depend on the precise nature of the groups R^{18} and R^{19} present in the compound of formula (V) and a number of variations

are possible. Thus for example when both of R^{18} and R^{19} are benzyl, hydrogenation of the product will yield the diacid of formula (I) wherein R^3 is CO_2R^4 and R and R^4 are both H. Alternatively if one of R^{18} and R^{19} is benzyl and the other is alkyl, hydrogenation will yield a monoester product. This can be hydrolysed, if desired, again to yield the diacid product. When one of R^{18} and R^{19} is t-butyl, treatment of the compound of formula (V) with trifluoroacetic acid yields the corresponding acid. The diester product wherein R^{18} and R^{19} are benzyl or lower alkyl can also be treated with trimethylsilyl iodide to produce the dicarboxylic acid product. If some other carboxylic acid protecting group is used for R^{18} or R^{19} then clearly appropriate conditions for its removal must be employed in the final step to give the ester or diacid product of formula (I). In the case where $R^{3'}$ is CH_2OH a single deprotection step is required to produce the compounds of formula (I) using deprotection methods as appropriate to the particular R^{18} group present in the compound of formula (V). In the case where the ring A or the substituent R^5 is unsaturated, the deprotection must be effected by non-reductive methods, thus for example if either of R and R^4 is benzyl, they may be removed by treatment with trimethylsilyl iodide.

As well as removing any protecting group which may be present in $R^{5'}$, a number of chemical transformation reactions are possible on the final mono-ester or diacid products as previously described. In each case the product may be obtained as the free carboxylic acid or it may be neutralised with an appropriate base and isolated in salt form.

In a variant of the above procedure, compounds of the formula (I) wherein R^5 is C_1-C_6 alkyl substituted by $-NR^8COR^9$, $-NR^8SO_2R^{10}$, $-NR^{11}COCR^{12}R^{13}R^{14}$ or $-NR^{11}SO_2CR^{12}R^{13}R^{14}$ are prepared by a process which involves acylating or sulphonylating a compound of the formula:



(VI)

wherein R^{20} is as defined for R^8 or R^{11}, R^{18} and $R^{3'}$ are as previously defined and Y is a C_1-C_6 alkyl group; by reaction with an acid of the formula R^9CO_2H, $R^{10}SO_3H$, $R^{12}R^{13}R^{14}CCO_2H$, or $R^{12}R^{13}R^{14}CSO_3H$, or an activated derivative thereof. The resulting amide or sulphonamide product is then deprotected if required and the mono- or diester product cleaved to yield the carboxylic acids of formula (I) wherein R is H and R^3 is CH_2OH or CO_2H as previously described.

The compounds of formula (VI) are prepared following the procedures shown in Scheme 1 but using a compound of formula (III) having $R^{5'}$ as a protected amine derivative. Thus, for example $R^{5'}$ can contain a bis-[(1S)-phenylethyl]aminomethyl substituent. Hydrogenation of the coupled product gives the corresponding free amine of formula (VI) wherein R^{20} is H and Y is CH_2. This route is of particular value for the preparation of compounds having 2(S) stereochemistry in the glutaramide backbone.

The starting cycloalkyl-substituted glutaric acid mono esters of formula III may be prepared as described in our European patent applications EP-A-0274234, 89305180.5 and 89304698.7.

The amines of formula (IV) are generally known compounds or they are prepared by appropriate synthetic procedures in accordance with literature precedents. Thus in one procedure the compounds of formula (IV) wherein R^3 is CH_2OH may be prepared by reduction of the corresponding acid, or lower alkyl ester for example using sodium borohydride.

Appropriate coupling and protecting methods for all of the above steps and alternative variations and procedures will be well known to those skilled in the art by reference to standard text books and to the examples provided hereafter.

As previously mentioned, the compounds of the invention are potent inhibitors of the neutral endopeptidase (E.C.3.4.24.11). This enzyme is involved in the breakdown of a number of peptide hormones and, in particular, it is involved in the breakdown of atrial natriuretic factor (ANF). This hormone consists of a family of related natriuretic peptides, secreted by the heart, of which the major circulating form in humans is known to be the 28 amino-acid peptide referred to as alpha-hANP. Thus, by preventing the degradation of ANF, by endopeptidase E.C.3.4.24.11, the compounds of the invention can potentiate its biological effects and the compounds are thus diuretic and natriuretic agents of utility in a number of disorders as previously described.

Activity against neutral endopeptidase E.C.3.4.24.11 is assessed using a procedure based on the assay described by J.T. Gafford, R.A. Skidgel, E.G. Erdos and L.B. Hersh, Biochemistry,

1983, 32, 3265-3271. The method involves determining the concentration of compound required to reduce by 50% the rate of release of radiolabelled hippuric acid from hippuryl-L-phenylalanyl-L-arginine by a neutral endopeptidase preparation from rat kidney.

The activity of the compounds as diuretic agents is determined by measuring their ability to increase urine output and sodium ion excretion in saline loaded conscious mice. In this test, male mice (Charles River CD1, 22-28 g) are acclimatised and starved overnight in metabowls. The mice are dosed intravenously via the tail vein, with the test compound dissolved in a volume of saline solution equivalent to 2.5% of body weight. Urine samples are collected each hour for two hours in pre-weighed tubes and analysed for electrolyte concentration. Urine volume and sodium ion concentration from the test animals are compared to a control group which received only saline.

For administration to man in the curative or prophylactic treatment of hypertension, congestive heart failure or renal insufficiency, oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2 to 400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier for administration singly, or in multiple doses, once or several times a day. Dosages for intravenous administration would typically be within the range 1 to 400 mg per single dose as required. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with

the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

The compounds may be administered alone but may also be administered together with such other agents as the physician shall direct to optimise control of blood pressure or to treat congestive heart failure, renal insufficiency or other disorders in any particular patient in accordance with established medical practice. Thus the compounds can be co-administered with a variety of cardiovascular agents, for example with an ACE inhibitor such as captopril or enalapril to facilitate the control of blood pressure in treatment of hypertension; or with digitalis,

or another cardiac stimulant, or with an ACE inhibitor, for the treatment of congestive heart failure. Other possibilities include co-administration with a calcium antagonist (e.g. nifedipine, amlodopine or diltiazem) a beta-blocker (e.g. atenolol) or an alpha-blocker (e.g. prazosin or doxazosin) as shall be determined by the physician as appropriate for the treatment of the particular patient or condition involved.

In addition to the above, the compounds may also be administered in conjunction with exogenous ANF, or a derivative thereof or related peptide or peptide fragment having diuretic/natriuretic activity or with other ANF-gene related peptides (e.g. as described by D. L. Vesely et al, Biochem. Biophys. Res. Comm., 1987, 143, 186).

Thus in a further aspect the invention provides a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, together with a pharmaceutically acceptable diluent or carrier.

The invention also includes a compound of the formula (I), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, for use in medicine, particularly for use as a diuretic agent for the treatment of hypertension, congestive heart failure or renal insufficiency in a human being.

The invention further includes the use of a compound of the formula (I) for the manufacture of a medicament for the treatment of hypertension, heart failure, angina, renal insufficiency, premenstrual syndrome, cyclical oedema, Menières disease, hyperaldosteronism, pulmonary oedema, ascites, hypercalciuria,

glaucoma, asthma, inflammation, pain, epilepsy, affective disorders, dementia and geriatric confusion, obesity, gastrointestinal disorders (including diarrhoea), hyperreninaemia, leukaemia, and the modulation of gastric acid secretion.

The preparation of the compounds of the invention will now be more particularly illustrated by reference to the following experimental Examples. The purity of compounds was routinely monitored by thin layer chromatography using Merck Kieselgel 60 F_{254} plates. ^1H-Nuclear magnetic reasonance spectra were recorded using a Nicolet QE-300 spectrometer and were in all cases consistent with the proposed structures.

EXAMPLE 1

2-{1-[2(R,S)-Carboxy-4-phenylbutyl]cyclopentylcarbonylamino)-2,3-dihydroindene-2-carboxylic acid

(a) 2-Amino-2,3-dihydroindene-2-carboxylic acid, benzyl ester

A mixture of 2-amino-2,3-dihydroindene-2-carboxylic acid hydrochloride (R. M. Pinder, B. H. Butcher, D. A. Buxton and D J Howells, J. Med. Chem., 1971, 14, 892), (11.33 g, 0.053 m), benzyl alcohol (27.5 ml, 0.27 m), para-toluenesulphonic acid monohydrate (12.1 g, 0.064 m) and benzene (150 ml) was boiled under reflux with continuous removal of water using a Dean-Stark trap. After 48 hours, further quantities of benzyl alcohol (27.5 ml, 0.27 m) and benzene (100 ml) were added, and the reaction allowed to continue under reflux for a further 72 hours. The cool reaction mixture was diluted with diethyl ether and the resulting white precipitate collected by filtration and washed with diethyl ether. The crude tosylate salt was then dissolved in water and this solution basified with 1M aqueous sodium hydroxide solution, then extracted with ethyl acetate. The combined extracts were washed with saturated brine, dried (anhydrous Na_2SO_4) and filtered. Evaporation under vacuum of the filtrate gave an oil (7.6 g, 53.6 %) which solidified at room temperature over-night. Crystallisation of a sample from hexane afforded the pure product as a white solid, m.p. 55-55.5°C. Found: C,75.98; H,6.38; N,5.18. $C_{17}H_{17}NO_2$ requires C,76.38; H,6.41; N,5.24%.

(b) 2-{1-[2(R,S)-Ethoxycarbonyl-4-phenylbutyl]cyclopentyl-carbonylamino}-2,3-dihydroindene-2-carboxylic acid, benzyl ester

Oxalyl chloride (470 mg, 3.74 mmol) was added at room temperature to a stirred solution of 1-[2(R,S)-ethoxycarbonyl-4-phenylbutyl]cyclopentane carboxylic acid (600 mg, 1.87 mmol) in dry dichloromethane (10 ml) containing dry dimethylformamide (2 drops). After 2 hours the solvent was removed under vacuum and the residual oxalyl chloride evaporated azeotropically using dry dichloromethane (3 x 10 ml).

The crude acid chloride was dissolved in dry dichloromethane (15 ml), then the resulting solution added dropwise to a stirred, ice-cold solution of the product from step (a) (500 mg, 1.87 mmol) and dry triethylamine (210 mg, 2.06 mmol) in dry dichloromethane (25 ml); stirring was continued for 1 hour at 0°C, then for 16 hours at room temperature. The reaction mixture was diluted with dichloromethane (60 ml), washed successively with water, 1M hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and water, dried (anhydrous Na_2SO_4) and filtered. Evaporation under vacuum of the filtrate afforded a brown gum (880 mg) which was purified by chromatography on silica gel using an ethyl acetate in hexane elution gradient (0-25%). Evaporation under vacuum of the appropriate fractions provided the required product as a clear oil, which subsequently formed a white waxy solid; crystallisation from diethyl ether-hexane gave the pure product (437 mg, 41.1%), m.p. 89-90°C. Found: C,76.21; H,7.22; N,2.48. $C_{36}H_{41}NO_5$ requires C,76.16; H,7.28; N,2.47%.

2-{1-[2(R,S)-Carboxy-4-phenylbutyl]cyclopentylcarbonylamino}-2,3-dihydroindene-2-carboxylic acid

(c) A 1M aqueous solution of sodium hydroxide (5 ml, 5 mmol) was added at room temperature to a stirred solution of the above product (430 mg, 0.76 mmole) in 1,4-dioxan (10 ml) and methanol (2.5 ml). After 5 days, the reaction mixture was diluted with water (40 ml), its pH adjusted to 7 with 2M hydrochloric acid, and the organic solvents removed by evaporation under vacuum. The resulting mixture was washed with diethyl ether, acidified to pH 2 with 2M hydrochloric acid, then extracted with ethyl acetate. The combined extracts were washed with saturated brine, dried (anhydrous Na_2SO_4), filtered, and evaporated under vacuum. Crystallisation of the residue from ethyl acetate-hexane gave the required product as a white solid (200 mg, 56.6%). Found: C,71.30; H,6.88; N.3.25. $C_{27}H_{31}NO_5$; 0.17 $CH_3CO_2C_2H_5$ requires C,71.59; H,7.02; N,3.02%.

EXAMPLE 2

2-{1-[2(R,S)-Carboxy-4-methoxybutyl]cyclopentylcarbonyl-amino)-2,3-dihydroindene-2-carboxylic acid

(a) 2-{1-[2(R,S)-Benzyloxycarbonyl-4-methoxybutyl]cyclopentyl-carbonylamino)-2,3-dihydroindene-2-carboxylic acid, benzyl ester

The procedure of Example 1(b) was followed using 1-[2(R,S)-benzyloxycarbonyl-4-methoxybutyl]cyclopentane carboxylic acid (334 mg, 1 mmole) and 2-amino-2,3-dihydroindene-2-carboxylic acid benzyl ester (267 mg, 1 mmol), to furnish the required diester (430 mg, 72.5%). Found: C,72.95; H,7.03; N,3.08. $C_{36}H_{41}NO_6$; 0.5 H_2O requires C,72.75; H,7.14; N,2.36%.

(b) 2-{1-[2(R,S)-Carboxy-4-methoxybutyl]cyclopentylcarbonylamino}-2,3-dihydroindene-2-carboxylic acid

A solution of the above product (390 mg, 0.67 mmol) in ethanol (20 ml) was hydrogenated over 10% palladium on charcoal (39 mg) at 15 p.s.i. (1 bar) and room temperature for 1 hour. The catalyst was removed by filtration through a pad of Arbocel (upper) and Hyflo (lower), then the filtrate evaporated under vacuum, and residual ethanol removed azeotropically with dichloromethane to provide the required product as a white solid (235 mg, 87.2%), m.p. 142-144°C. Found: C,65.17; H,7.29; N,3.32. $C_{22}H_{29}NO_6$ requires C,65.49; H,7.25; N,3.47%.

EXAMPLE 3

2-{1-[2(R,S)-Carboxy-3-(S-lysylamino)propyl]cyclopentylcarbonylamino}-2,3-dihydroindene-2-carboxylic acid

(a) 2-Amino-2,3-dihydroindene-2-carboxylic acid, ethyl ester, hydrochloride

A stirred, ice-cold solution of 2-amino-2,3-dihydroindene-2-carboxylic acid hydrochloride (2.48 g, 11.6 mmol) in absolute ethanol was saturated with dry hydrogen chloride. The resulting suspension was stirred at room temperature overnight, then warmed to 40°C and treated further with dry hydrogen chloride until a clear solution was obtained (2 hours). After a further 4 hours at 40°C, the reaction mixture was evaporated to dryness under vacuum, then the residue crystallised from ethanol-diethyl ether to give the pure product (2.41 g, 85.8%), m.p. 189-193°C. Found: C,59.74; H,6.69; N,5.76. $C_{12}H_{15}NO_2$; HCl requires C,59.63; H,6.67; N,5.79%.

(b) 2-{1[2(R,S)-tert-Butoxycarbonyl-3-(dibenzylamino)propyl]-cyclopentylcarbonylamino}-2,3-dihydroindene-2-carboxylic acid, ethyl ester

To a stirred, ice-cold solution of 2(R,S)-tert-butoxycarbonyl-3-(dibenzylamino)propylcyclopentane carboxylic acid hydrochloride (7.84 g, 0.016 m), 1-hydroxybenzotriazole (2.16 g, 0.016 m) and 4-methylmorpholine (4.86 g, 0.048 m) in dry dichloromethane (100 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.13 g, 0.032 m); stirring was continued for 1 hour at 0°C, then for 16 hours at room temperature. The dichloromethane was removed by evaporation under vacuum at room temperature, and the residue partitioned between diethyl ether and water. The ether phase was separated, washed with water, dried (anhydrous Na_2SO_4) and filtered; subsequent evaporation under vacuum at room temperature of the filtrate provided the crude activated ester (9.33 g, 95.4%) as a hemi-solvate with dichloromethane, of sufficient purity for further progression.

To a stirred solution of this activated ester (3.24 g, 5.3 mmol) in dry dichloromethane (40 ml) at 0°C was added 2-amino-2,3-dihydroindene-2-carboxylic acid ethyl ester (1.09 g, 5.3 mmol) and 4-dimethylaminopyridine (0.71 g, 5.8 mmol). After 0.5 hours the solvent was removed by evaporation under vacuum and the resulting viscous oil allowed to stand at room temperature for 3 days before partitioning between diethyl ether and water. The ether phase was separated, washed with water, dried (anyhdrous $MgSO_4$) and filtered. Evaporation under vacuum of the filtrate furnished an oil which was purified by chromatography on silica gel using a dichloromethane in hexane elution gradient (20-100%).

Evaporation of the appropriate fractions provided the required product (2.10 g, 61.2%). Found: C,73.92; H,7.88; N,4.55. $C_{40}H_{50}N_2O_5$ 0.5 H_2O requires C,74.15; H,7.94; N,4.33%.

(c) 2-{1-[3-Amino-2(R,S)-tert-butoxycarbonylpropyl]cyclopentyl-carbonylamino}-2,3-dihydroindene-2-carboxylic acid, ethyl ester

A solution of the above diester (2.7 g, 4.2 mmol) in a mixture of ethanol (6 ml) and water (0.5 ml) was hydrogenated over 20% palladium hydroxide on charcoal (270 mg) at 50 p.s.i. (3.45 bar) and room temperature for 16 hours. The catalyst was removed by filtration through a pad of Arbocel (upper) and Hyflo (lower), then the filtrate evaporated under vacuum, and residual solvents removed azeotropically with dichloromethane, to afford the required product (1.92 g, 99.6%). Found: C,67.64; H,8.44; N,5.89. $C_{26}H_{38}N_2O_5$ requires C,68.09; H,8.35; N,6.11%.

(d) 2-{1-[2(R,S)-tert-Butyloxycarbonyl-3-(N^2, N^6-di-benzyloxy-carbonyl-S-lysyl-amino)propyl]cyclopentylcarbonylamino}-2,3-dihydroindene-2-carboxylic acid, ethyl ester

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (944 mg, 4.92 mmol) was added to a stirred solution of the above amine (1.13 g, 2.46 mmol), 1-hydroxybenzotriazole (322 mg, 2.46 mmol), N^2, N^6-di-benzyloxycarbonyl-S-lysine (1.02 g, 2.46 mmol) and 4-methylmorpholine (746 mg, 7.38 mmol) in dry dichloromethane (25 ml) at 0°C. Stirring was continued for 0.5 hours at 0°C, then for 16 hours at room temperature, before removal of the solvent under vacuum. The residue was partitioned between diethyl ether and water, then the ether phase washed with 1M hydrochloric acid and water, dried (anhydrous Na_2SO_4) and filtered. Evaporation under vacuum of the filtrate, followed by chromatography of the

residual oil on silica gel using a diethyl ether in hexane elution gradient (0-50%), gave the required product (1.30 g, 61.8%). Found: C,67.31; H,7.40; N,6.09. $C_{48}H_{62}N_4O_{10}$ requires C,67.42; H,7.31; N,6.55%.

(e) 2-{1-[2(R,S)-Carboxy-3-(N^2, N^6-di-benzyloxycarbonyl-S-lysyl-amino)propyl]cyclopentylcarbonylamino}-2,3-dihydroindene-2-carboxylic acid, ethyl ester

Trifluoroacetic acid (5 ml) was added dropwise to a stirred solution of the above product (1.28 g, 1.5 mmol) in dry dichloromethane (10 ml) at 0°C. The ice-bath was removed, stirring continued for 1 hour at room temperature, then the reaction mixture evaporated under vacuum. The crude product was dissolved in ethyl acetate and residual trifluoroacetic acid removed by washing the solution with saturated aqueous sodium bicarbonate solution. Drying (anhydrous Na_2SO_4), filtration and evaporation under vacuum of the ethyl acetate solution, followed by azeotropic removal of residual solvent with dichloromethane, afforded the required product (1.12 g, 90.4%). Found: C,63.85; H,6.66; N,6.59. $C_{44}H_{54}N_4O_{10}$; 1.5 H_2O requires C,63.98; H,6.96; N,6.78%.

(f) 2-{1-[2(R,S)-Carboxy-3-(S-lysylamino)propyl]cyclopentyl-carbonylamino}-2,3-dihydroindene-2-carboxylic acid, ethyl ester

A solution of the above product (1.10 g, 1.33 mmol) in a mixture of ethanol (7 ml) and water (0.5 ml) was hydrogenated over 10% palladium on charcoal (110 mg) at 60 p.s.i. (4.1 bar) and room temperature for 16 hours. Work-up as described above for Example 2 (b) provided the required product as a beige foam (740 mg, 98.9%). Found: C,59.98; H,7.56; N,9.52. $C_{28}H_{42}N_4O_6$; 1.75 H_2O requires C,59.82; H,8.16; N,9.97%.

(g) 2-{1-[2(R,S)-Carboxy-3-(S-lysylamino)propyl]cyclopentylcarbonylamino}-2,3-dihydroindene-2-carboxylic acid

A solution of the above ester (700 mg, 1.24 mmol) in 1M aqueous sodium hydroxide solution (7.5 ml, 7.5 mmol) was allowed to stand at room temperature for 16 hours, then loaded onto a column of strongly acidic ion-exchange resin. The column was washed to neutrality using distilled water, then eluted with 5% aqueous pyridine. Evaporation under vacuum of the appropriate fractions gave a glass which was dissolved in distilled water; freeze drying of this aqueous solution provided the required product (370 mg, 55.4%). Found: C,57.58; H,7.95; N,10.31. $C_{26}H_{38}N_4O_6$; $2H_2O$ requires C,57.97; H,7.86; N,10.40%.

EXAMPLE 4

2-{1-[3-(N^2-Acetyl-S-lysylamino)-2(R,S)-carboxypropyl]cyclopentylcarbonylamino}-2,3-dihydroindene-2-carboxylic acid

The procedure of Example 3 was followed but using N^2-acetyl-N^6-benzyloxycarbonyl-S-lysine in step (d). Deprotection gave the title compound. Found: C,58.30; H,7.58; N,10.07. $C_{28}H_{40}N_4O_7$; 1.75 H_2O requires C,58.36; H,7.61; N,9.72%.

EXAMPLE 5

2-{1-[2(R,S)-Carboxy-3-(N^2-methanesulphonyl-S-lysylamino)-propyl]cyclopentylcarbonylamino}-2,3-dihydroindene-2-carboxylic acid

The procedure of Example 3 was followed but using N^6-benzyloxycarbonyl-N^2-methanesulphonyl-S-lysine in step (d). Deprotection gave the title compound. Found: C,53.99; H,7.13; N,9.31. $C_{27}H_{40}N_4O_8S$; H_2O requires C,54.17; H,7.07; N,9.36%.

EXAMPLE 6

2-{1-[2(S)-Carboxy-3-(S-lysylamino)propyl]cyclopentyl-carbonylamino}-2,3-dihydroindene-2-carboxylic acid

(a) 2-{1-[2(S)-tert-Butoxycarbonyl-3-{(S,S)-alpha, alpha^1-dimethyldibenzylamino}propyl]cyclopentylcarbonylamino}-2,3-dihydroindene-2-carboxylic acid, ethyl ester

The procedure of Example 3 was followed but using 1-{2(S)-tert-butoxycarbonyl-3-[(S,S)-alpha, alpha^1-1-dimethyldibenzyl-amino)propyl]cyclopentane carboxylic acid in step (b) to give the title product, in 79.1% yield. Found: C, 75.45; H,8.30; N,4.01. $C_{42}H_{54}N_2O_5$ requires C,75.64; H,8.16; N,4.20%.

(b) 2-{1-[3-Amino-2(S)-tert-butoxycarbonylpropyl]cyclopentyl-carbonylamino}-2,3-dihydroindene-2-carboxylic acid, ethyl ester

Hydrogenation of the above product as described in Example 3(c) gave the 2(S) isomer of the amine in 99.1% yield. Rf (silica) 0.50 (dichloromethane-methanol, 9:1).

(c) 2-{1-[2(S)-Carboxy-3-(S-lysylamino)propyl]cyclopentyl-carbonylamino}-2,3-dihydroindene-2-carboxylic acid

The above amine was coupled to N^2, N^6-di-benzyloxycarbonyl-S-lysine following the procedure of Example 3(d) and the product deprotected as described in Example 3 steps (e) to (g) to give the title compound. Found: C,56.71; H,7.48; N,9.16. $C_{26}H_{38}N_4O_6$; 2.5 H_2O requires C,57.02; H,7.91; N,10.23%.

EXAMPLE 7

2-{1-[2(S)-Carboxy-3-(N^2-methanesulphonyl-S-lysylamino)-propyl]cyclopentylcarbonylamino}-2,3-dihydroindene-2-carboxylic acid

The procedure of Example 6 was followed but using N^6-benzyloxy-carbonyl-N^2-methanesulphonyl-S-lysine in the coupling step to give the title compound. Found: C,53.60; H,7.27; N,8.82. $C_{27}H_{40}N_4O_8S$; 1.5 H_2O requires C,53.36; H,7.13; N,9.22%.

EXAMPLE 8

2-{1-[2(R,S)-Carboxypentyl]cyclopentylcarbonylamino}-2-hydroxymethyl-2,3-dihydroindene

(a) 2-Amino-2-hydroxymethyl-2,3-dihydroindene

A solution of 2-amino-2,3-dihydroindene-2-carboxylic, ethyl ester, hydrochloride (1.7 g, 7.03 mmol) in 50% aqueous ethanol (15 ml), was added dropwise to a stirred, ice-cold solution of sodium borohydride (1.11 g, 29.4 mmol) in 50% aqueous ethanol (35 ml), then the reaction mixture heated under reflux for 3 hours.

The bulk of the ethanol was removed by evaporation under vacuum, and the residual suspension saturated with sodium chloride then extracted with ethyl acetate. The combined extracts were washed with saturated brine, dried (anhydrous $MgSO_4$), filtered and evaporated under vacuum. Crystallisation of the resulting white solid (1.05 g) from ethyl acetate-hexane afforded the required product (0.99 g, 84.8%), m.p. 89.5-90.5°C. Found: C,72.32; H,8.02; N,8.17. $C_{10}H_{13}NO$; 0.15 H_2O requires C,72.39; H,8.08; N,8.44%.

(b) 2-{1[(R,S)-Benzyloxycarbonylpentyl]cyclopentylcarbonylamino}-2-hydroxymethyl-2,3-dihydroindene

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (767 mg, 4 mmol) was added to a stirred, ice-cold mixture of 1-[2(R,S)-benzyloxycarbonylpentyl]cyclopentane carboxylic acid (637 mg, 2 mmol), 1-hydroxybenzotriazole (270 mg, 2 mmol), 4-methylmorpholine (202 mg, 2 mmol), the product from step (a) above (332 mg, 2 mmol) and dry dichloromethane (10 ml). Stirring was continued for 0.5 hours at 0°C, then for 24 hours at room temperature.

The dichloromethane was removed by evaporation under vacuum, and the residue partitioned between diethyl ether and water. The ether phase was separated, washed with water, 1M hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and water, then dried (anhydrous $MgSO_4$) and filtered. Evaporation under vacuum of the filtrate furnished an oil which was purified by chromatography on silica gel using diethyl ether-hexane (1:1) as eluent. Evaporation under vacuum of the appropriate fractions provided the required product (180 mg, 19.0%). Found: C,73.75; H,7.84; N,3.06. $C_{29}H_{37}NO_4$; 0.5 H_2O requires C,73.69; H,8.10; N,2.96%.

(c) 2-{1-[2(R,S)-Carboxypentyl]cyclopentylcarbonylamino}-2-hydroxymethyl-2,3-dihydroindene

A solution of the above product (170 mg, 0.36 mmol) in a mixture of ethanol (20 ml) and water (1 ml), was hydrogenated over 5% palladium on charcoal at 50 p.s.i. (3.45 bar) and room temperature, to give the title product as a white solid (115 mg, 83.5%), m.p. 126-128°C, after trituration with diethyl ether-hexane (1:1). Found: C,69.04; H,8.15; N,3.63. $C_{22}H_{31}NO_4$; 0.5 H_2O requires C,69.08; H,8.43; N,3.66%.

EXAMPLE 9

2-{1-[2(R,S)-Carboxy-4-phenylbutyl]cyclopentylcarbonylamino}-2-hydroxymethyl-2,3-dihydroindene

(a) 2-{1-[2(R,S)-Benzyloxycarbonyl-4-phenylbutyl]cyclopentylcarbonylamino}-2-hydroxymethyl-2,3-dihydroindene

The procedure of Example 8(b) was followed using 1-[2(R,S)-benzyloxycarbonyl-4-phenylbutyl]cyclopentanecarboxylic acid as starting material and allowing the reaction mixture to stand at room temperature for a further 5 days. The required product was obtained as an oil (19.9%). Rf (silica) 0.15 (diethyl ether-hexane, 1:1).

(b) 2-{1-[2(R,S)-Carboxy-4-phenylbutyl]cyclopentylcarbonylamino}-2-hydroxymethyl-2,3-dihydroindene

Hydrogenation of the above product as described in Example 8(c), followed by chromatography on silica gel using ethyl acetate as eluent and evaporation under vacuum of the appropriate fractions, followed by trituration of the residue with diethyl ether-hexane (1:4), gave the required product (62.4%) as a white solid, m.p. 140-143°C. Found: C,73.76; H,7.62; N,3.12. $C_{27}H_{33}NO_4$; 1/4 H_2O requires C,73.69; H,7.67; N,3.18%.

EXAMPLE 10

2-{1-[2(R,S)-Carboxy-3-(S-lysylamino)propyl]cyclopentylcarbonylamino}-2-hydroxymethyl-2,3-dihydroindene

(a) 2-{1-[2(R,S)-tert-Butoxycarbonyl-3-(dibenzylamino)propyl]cyclopentylcarbonylamino}-2-hydroxymethyl-2,3-dihydroindene

4-Methylmorpholine (1.78 g, 17.6 mmol) was added to a stirred solution of the N-hydroxybenzotriazole-derived activated ester

hemi-solvate with dichloromethane of 2(R,S)-tert-butoxycarbonyl-3-(dibenzylamino)propylcyclopentane carboxylic acid (Example 3b) (9.78 g, 16 mmol) and 2-amino-2-hydroxymethyl-2,3-dihydroindene (2.65 g, 16 mmol) in dry dichloromethane (50 ml) at room temperature. After 2 hours the solvent was removed by evaporation under vacuum and the residue allowed to stand at room temperature for 2 days before being partitioned between diethyl ether and water. The ether phase was separated, washed with water, dried (anhydrous $MgSO_4$) and filtered. Evaporation under vacuum of the filtrate, followed by purification of the residue by chromatography on silica gel using a dichloromethane in hexane elution gradient (20-100%), afforded the required product (3.30 g, 33.6%). Found: C,75.09; H,8.02; N,4.69. $C_{38}H_{48}N_2O_4$, 0.2 CH_2Cl_2 requires C,74.75; H,7.95; N,4.57%.

(b) 2-{1-[3-Amino-2(R,S)-tert-butoxycarbonylpropyl]cyclopentyl-carbonylamino}-2-hydroxymethyl-2,3-dihydroindene

The above product was hydrogenated as described in Example 3(c) to give the title amine in 98.2% yield. Found: C,68.96; H,8.88; N,6.63. $C_{24}H_{36}N_2O_4$ requires C,69.20; H,8.71; N,6.73%.

(c) 2-{1-[2(R,S)-tert-Butoxycarbonyl-3-(N^2, N^6-di-benzyloxy-carbonyl-S-lysylamino)propyl]cyclopentylcarbonylamino}-2-hydroxy-methyl-2,3-dihydroindene

The above amine was coupled to N^2, N^6-dibenzyloxycarbonyl-S-lysine following the procedure of Example 3(d) but using a gradient of diethyl ether-hexane (1:8 to 1:1) followed by ethyl acetate as eluents for chromatographic purification to give the product in 62.0% yield. Found: C,67.59; H,7.53; N,6.75. $C_{46}H_{60}N_4O_9$ requires C,67.96; H,7.44; N,6.89%.

(d) 2-{1-[2(R,S)-Carboxy-3-(N^2, N^6-di-benzyloxycarbonyl-S-lysyl-amino)propyl]cyclopentylcarbonylamino}-2-hydroxymethyl-2,3-dihydroindene

A stirred, ice-cold solution of the above product (1.24 g, 1.52 mmol) in dry dichloromethane (20 ml) was saturated with dry hydrogen chloride. After a further 2 hours at 0°C, the reaction mixture was evaporated under vacuum and the residue azeotroped with dichloromethane to provide the title product as a white foam (1.05 g, 85.3%). Found: C,64.28; H,6.83; N,7.21. $C_{42}H_{52}N_4O_9$; 1.5 H_2O requires C,64.35; H,7.07; N,7.15%.

(e) 2-{1-[2(R,S)-Carboxy-3-(S-lysylamino)propyl]cyclopentyl-carbonylamino}-2-hydroxymethyl-2,3-dihydroindene

The above product was hydrogenated following the procedure of Example 3(f) to give the required title acid as a white foam (79.7%). Found: C,61.20; H,8.14; N,10.41. $C_{26}H_{40}N_4O_5$; 1.25 H_2O requires C,61.09; H,8.38; N,10.96%.

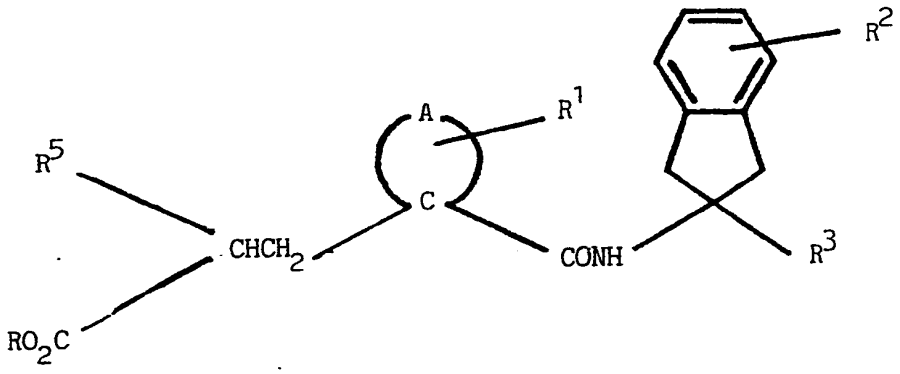
EXAMPLE 11

2-{1-[2(S)-Carboxy-3-(N^2-methanesulphonyl-S-lysylamino)-propyl]cyclopentylcarbonylamino}-2-hydroxymethyl-2,3-dihydroindene

The procedure of Example 10 was followed but using the N-hydroxybenzotriazole-derived activated ester of 2(S)-tert-butyloxycarbonyl-3-[(S,S)-alpha, $alpha^1$-dimethyldibenzylamino]-propylcyclopentane carboxylic acid as starting material in step (a) and coupling with N^6-tert-butyloxycarbonyl-N^2-methane-sulphonyl-S-lysine in step (c). Deprotection as previously described gave the product which was dissolved in a little distilled water and freeze dried to give the title product as a white solid. Found: C,51.50; H,7.38; N,8.67. $C_{27}H_{42}N_4O_7S$; HCl; 1.5 H_2O requires C,51.46; H,7.36; N,8.89%.

CLAIMS

1. A compound having the formula-:



(I)

wherein A completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring ;

R is H, C_1-C_6 alkyl, benzyl or an alternative biolabile ester-forming group;

R^1 is H or C_1-C_4 alkyl;

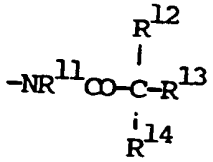
R^2 is H, OH, C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or CF_3;

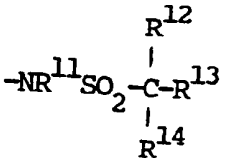
R^3 is CH_2OH or CO_2R^4 wherein R^4 is as previously defined for R;

and R^5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkenyl,

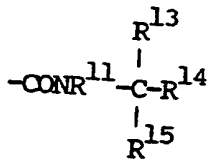
or R^5 is C_1-C_6 alkyl substituted by halo, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkoxy(C_1-C_6)alkoxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, aryl, aryloxy, heterocyclyl, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^{10}$, $-CONR^6R^7$ or R^6R^7N-(C_1-C_6)alkoxy;

or R^5 is C_1-C_6 alkyl substituted by a group of the formula:





or



wherein R^6 and R^7 are each independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, aryl, aryl(C_1-C_4)alkyl, C_2-C_6 alkoxyalkyl, or heterocyclyl; or the two groups R^6 and R^7 are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C_1-C_4)alkyl-piperazinyl group;

R^8 is H or C_1-C_4 alkyl;

R^9 is C_1-C_4 alkyl, CF_3, aryl, aryl(C_1-C_4)alkyl, aryl(C_1-C_4)alkoxy, heterocyclyl, C_1-C_4 alkoxy or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{10} is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, aryl or heterocyclyl;

R^{11} is H, C_1-C_6 alkyl, aryl or C_3-C_7 cycloalkyl;

R^{12} is $R^{11}CONR^{11}$-, $R^{11}SO_2NR^{11}$-, $R^{16}R^{17}N$-$(CH_2)_p$-, or $R^{11}O$-, wherein each R^{11} is as previously defined above;

R^{13} and R^{14} are each independently H or C_1-C_6 alkyl; or

R^{13} is H and R^{14} is C_1-C_6 alkyl which is substituted by OH, C_1-C_4 alkoxy, SH, SCH_3, NH_2, aryl(C_1-C_6)alkyl-OCONH-, NH_2CO-, CO_2H, guanidino, aryl, or heterocyclyl; or the two groups R^{13} and R^{14} are joined together to form, with the carbon atom to which they are attached, a 5 or 6 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be substituted by C_1-C_4 alkyl or fused to a further 5 or 6 membered saturated or unsaturated carbocyclic ring;

or R^{13} is H, and R^{12} and R^{14} are linked to form a 2-(N-COR^{11}-4-aminopyrrolidinyl) group;

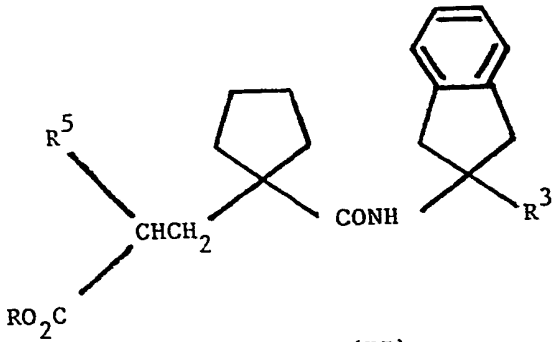
R^{15} is $R^{16}R^{17}NCO$-, $R^{11}OCO$-, $R^{11}OCH_2$- or heterocyclyl, wherein R^{11} is as previously defined above;

R^{16} and R^{17} are each independently H or C_1-C_6 alkyl;

and p is 0 or an integer of from 1 to 6;

and pharmaceutically acceptable salts thereof and bioprecursors therefor.

2. A compound according to claim 1 wherein A is $(CH_2)_4$ and R^1 and R^2 are H having the formula



(II)

wherein R, R^3 and R^5 are as previously defined for formula (I).

3. A compound as claimed in claim 1 or claim 2 wherein R is H, R^3 is CO_2R^4 and R^4 is H.

4. A compound as claimed in claim 1 or claim 2 wherein R^3 is CO_2R^4 and one or both of R and R^4 is a biolabile ester-forming group and said group is ethyl, benzyl,1-(2,2-diethyl-butyryloxy)-ethyl, 2-ethylpropionyloxymethyl, 1-(2-ethyl-propionyloxy)ethyl, 1-(2,4-dimethylbenzoyloxy)ethyl, 1-(benzoyloxy)benzyl, 1-(benzoyloxy)ethyl, 2-methyl-1-propionyloxypropyl, 2,4,6-trimethyl-benzoyloxymethyl, 1-(2,4,6-trimethyl-benzyloxy)ethyl, pivaloyloxymethyl, phenethyl, phenpropyl, 2,2,2-trifluoroethyl, 1- or 2-naphthyl, 2,4-dimethyl-phenyl, 4-t-butyl-phenyl, 5-(4-methyl-1,3-dioxolenyl-2-onyl)-methyl or 5-indanyl.

5. A compound as claimed in any one of claims 1 to 4 wherein R^5 is methylene substituted by a group of the formula $-NHCOCR^{12}R^{13}R^{14}$, and R^{12} is NH_2, $R^{11}CONH-$ or $R^{11}SO_2NH-$, R^{13} is H and R^{14} is $-(CH_2)_4NH_2$.

6. A compound as claimed in any one of claims 1 to 4 wherein R^5 is C_1-C_6 alkyl, C_1-C_6 alkyl substituted by C_1-C_6 alkoxy or C_1-C_6 alkyl substituted by phenyl.

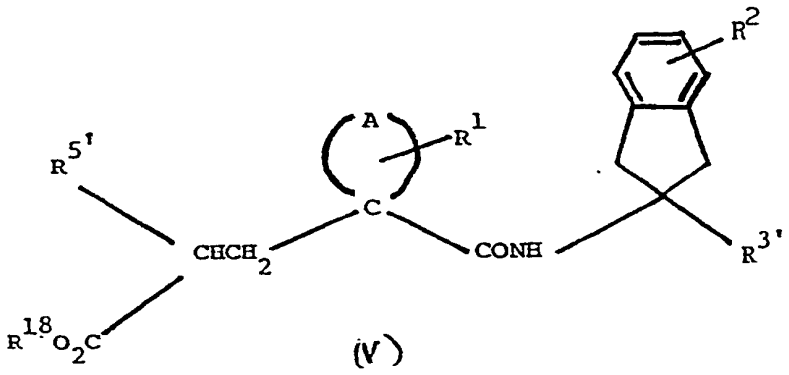
7. A compound according to claim 1 wherein said compound is-:

2-(1-[2(S)-carboxy-3-(S-lysylamino)propyl]cyclopentyl-carbonylamino)-2,3-dihydroindene-2-carboxylic acid,

2-(1-[2(S)-carboxy-3-(N^2-methanesulphonyl-S-lysylamino)-propyl]cyclopentylcarbonylamino)-2,3-dihydroindene-2-carboxylic acid, or

2-{1-[2(S)-carboxy-3-(N^2-methanesulphonyl-S-lysylamino)-propyl]cyclopentylcarbonylamino)-2-hydroxymethyl-2,3-dihydroindene; or a biolabile ester derivatives thereof.

8. A process for preparing a compound of the formula (I) as claimed in claim 1 which comprises subjecting a compound of the formula-:



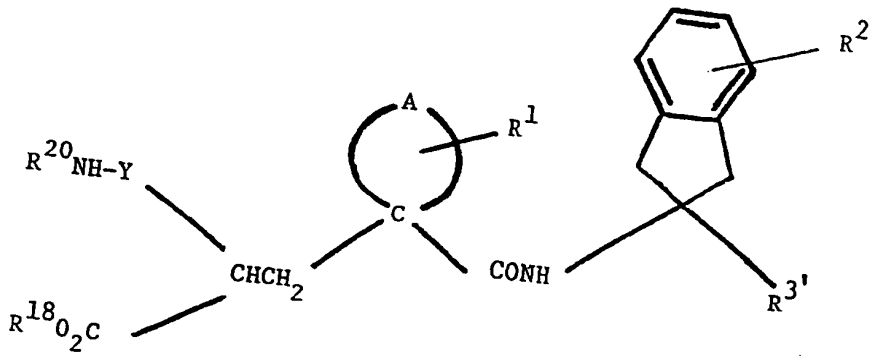
(V)

wherein A, R^1 and R^2 are as previously defined, $R^{5'}$ is as defined for R^5 with any reactive group therein protected if necessary, R^{18} is as defined for R excluding H, or is a conventional carboxylic acid protecting group, and $R^{3'}$ is either CH_2OH or CO_2R^{19} wherein R^{19} is as previously defined for R^4 excluding H or is a conventional carboxylic acid protecting group;

to a hydrolysis and/or hydrogenation and/or other deprotection reaction to remove any protective group present in $R^{5'}$ and to remove one or both of R^{18} and R^{19}, if present, to yield the corresponding dicarboxylic acid of formula (I) wherein R and R^4 are both H, or to yield the corresponding mono-ester product

wherein one of R and R^4 is H and the other is a biolabile ester-forming group; or in the case where $R^{3'}$ is CH_2OH, to yield the mono-carboxylic acid where R is H; and optionally forming a pharmaceutically acceptable salt of the product.

9. A process for preparing a compound of the formula (I) wherein R^5 is C_1-C_6 alkyl substituted by $-NR^8COR^9$, $-NR^8SO_2R^{10}$, $-NR^{11}COCR^{12}R^{13}R^{14}$ or $-NR^{11}SO_2CR^{12}R^{13}R^{14}$ which comprises acylating or sulphonating a compound of the formula:



(VI)

wherein R^{20} is as defined for R^8 or R^{11}, R^{18} and $R^{3'}$ are as previously defined and Y is a C_1-C_6 alkyl group; by reaction with an acid of the formula R^9CO_2H, $R^{10}SO_3H$, $R^{12}R^{13}R^{14}CCO_2H$, or $R^{12}R^{13}R^{14}CSO_3H$, or an activated derivative thereof, followed by deprotection if required and hydrogenation or hydrolysis of the mono- or diester product to yield the carboxylic acid of formula (I) wherein R is H and R^3 is CH_2OH or CO_2H, and optionally forming a pharmaceutically acceptable salt of the product.

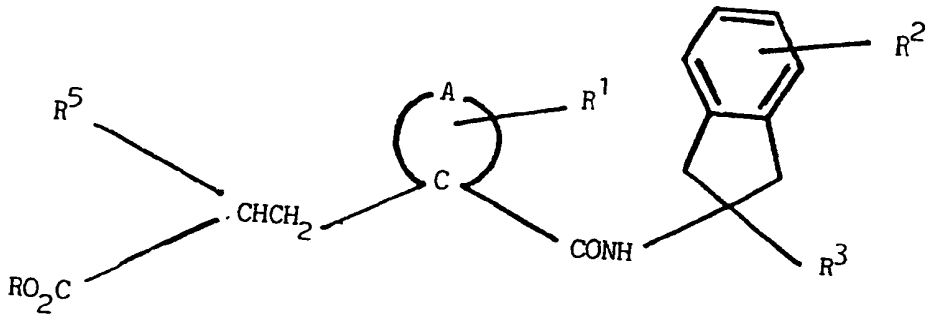
10. A process as claimed in claim 8 or claim 9 wherein R^{18} and

R^{19} are independently selected from t-butyl, ethyl and benzyl and said groups are removed by treatment with trifluoroacetic acid, aqueous alkali or catalytic hydrogenation respectively, to yield the compound of formula (I) wherein R and R^4 (if present) are both H.

11. A pharmaceutical composition comprising a compound of the formula (I) or (II) as claimed in any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof or bioprecursor therefor, together with a pharmaceutically acceptable diluent or carrier.

12. A compound of the formula (I) or (II) as claimed in any of claims 1 to 7 or a pharmaceutically acceptable salt thereof or bioprecursor therefor, for use in medicine, particularly for the treatment of hypertension, heart failure or renal insufficiency.

13. A process for preparing a compound having the formula-:



(I)

wherein A completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring ;

R is H, C_1-C_6 alkyl, benzyl or an alternative biolabile ester-forming group;

R^1 is H or C_1-C_4 alkyl;

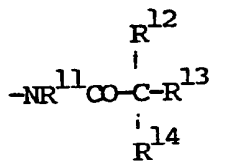
R^2 is H, OH, C_1-C_4 alkyl, C_1-C_4 alkoxy, halo or CF_3;

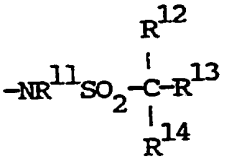
R^3 is CH_2OH or CO_2R^4 wherein R^4 is as previously defined for R;

and R^5 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkenyl,

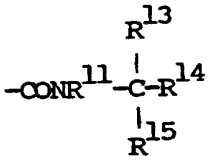
or R^5 is C_1-C_6 alkyl substituted by halo, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkoxy(C_1-C_6)alkoxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, aryl, aryloxy, heterocyclyl, $-NR^6R^7$, $-NR^8COR^9$, $-NR^8SO_2R^{10}$, $-CONR^6R^7$ or R^6R^7N-(C_1-C_6)alkoxy;

or R^5 is C_1-C_6 alkyl substituted by a group of the formula:





or



wherein R^6 and R^7 are each independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, aryl, aryl(C_1-C_4)alkyl, C_2-C_6 alkoxyalkyl, or heterocyclyl; or the two groups R^6 and R^7 are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C_1-C_4)alkyl-piperazinyl group;

R^8 is H or C_1-C_4 alkyl;

R^9 is C_1-C_4 alkyl, CF_3, aryl, aryl(C_1-C_4)alkyl, aryl(C_1-C_4)alkoxy, heterocyclyl, C_1-C_4 alkoxy or NR^6R^7 wherein R^6 and R^7 are as previously defined;

R^{10} is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, aryl or heterocyclyl;

R^{11} is H, C_1-C_6 alkyl, aryl or C_3-C_7 cycloalkyl;

R^{12} is $R^{11}CONR^{11}$-, $R^{11}SO_2NR^{11}$-, $R^{16}R^{17}N$-$(CH_2)_p$-, or $R^{11}O$-, wherein each R^{11} is as previously defined above;

R^{13} and R^{14} are each independently H or C_1-C_6 alkyl; or

R^{13} is H and R^{14} is C_1-C_6 alkyl which is substituted by OH, C_1-C_4 alkoxy, SH, SCH_3, NH_2, aryl(C_1-C_6)alkyl-OCONH-, NH_2CO-, CO_2H, guanidino, aryl, or heterocyclyl; or the two groups R^{13} and R^{14} are joined together to form, with the carbon atom to which they are attached, a 5 or 6 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be substituted by C_1-C_4 alkyl or fused to a further 5 or 6 membered saturated or unsaturated carbocyclic ring;

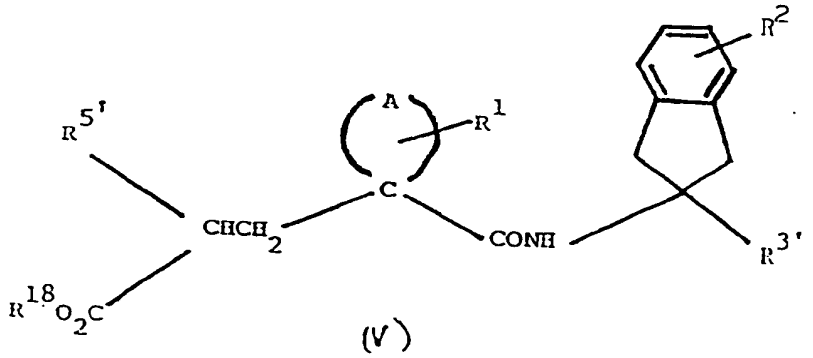
or R^{13} is H, and R^{12} and R^{14} are linked to form a 2-(N-COR^{11}-4-aminopyrrolidinyl) group;

R^{15} is $R^{16}R^{17}NCO$-, $R^{11}OCO$-, $R^{11}OCH_2$- or heterocyclyl, wherein R^{11} is as previously defined above;

R^{16} and R^{17} are each independently H or C_1-C_6 alkyl;

and p is 0 or an integer of from 1 to 6;

which comprises subjecting a compound of the formula:

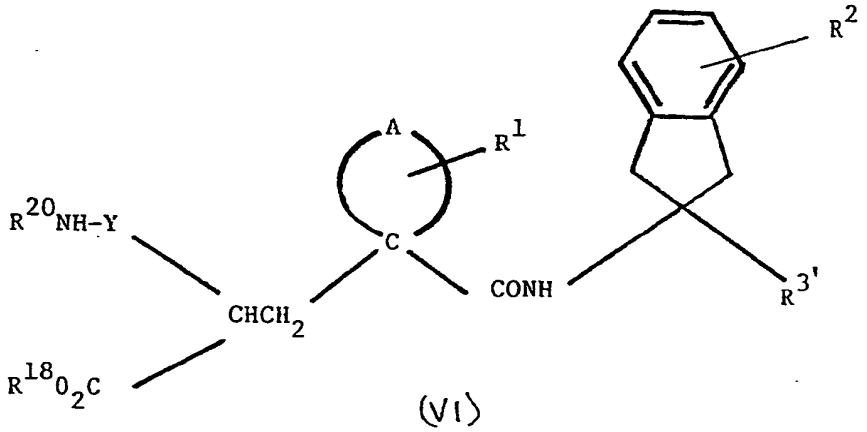


(V)

wherein A, R^1 and R^2 are as previously defined, $R^{5'}$ is as defined for R^5 with any reactive group therein protected if necessary, R^{18} is as defined for R excluding H, or is a conventional carboxylic acid protecting group, and $R^{3'}$ is either CH_2OH or CO_2R^{19} wherein R^{19} is as previously defined for R^4 excluding H or is a conventional carboxylic acid protecting group;

to a hydrolysis and/or hydrogenation and/or other deprotection reaction to remove any protective group present in $R^{5'}$ and to remove one or both of R^{18} and R^{19}, if present, to yield the corresponding dicarboxylic acid of formula (I) wherein R and R^4 are both H, or to yield the corresponding mono-ester product wherein one of R and R^4 is H and the other is a biolabile ester-forming group; or in the case where $R^{3'}$ is CH_2OH, to yield the mono-carboxylic acid where R is H, and optionally forming a pharmaceutically acceptable salt of the product.

14. A process for preparing a compound of the formula (I) wherein R^5 is C_1-C_6 alkyl substituted by $-NR^8COR^9$, $-NR^8SO_2R^{10}$, $-NR^{11}COCR^{12}R^{13}R^{14}$ or $-NR^{11}SO_2CR^{12}R^{13}R^{14}$ which comprises acylating or sulphonating a compound of the formula:

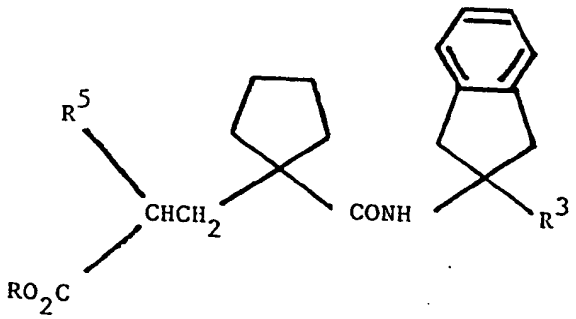


(VI)

wherein R^{20} is as defined for R^8 or R^{11}, R^{18} and $R^{3'}$ are as previously defined and Y is a C_1-C_6 alkyl group; by reaction with an acid of the formula R^9CO_2H, $R^{10}SO_3H$, $R^{12}R^{13}R^{14}CCO_2H$, or $R^{12}R^{13}R^{14}CSO_3H$, or an activated derivative thereof, followed by deprotection if required and hydrogenation or hydrolysis of the mono- or diester product to yield the carboxylic acid of formula (I) wherein R is H and R^3 is CH_2OH or CO_2H; and optionally forming a pharmaceutically acceptable salt of the product.

15. A process as claimed in claim 13 or claim 14 wherein R^{18} and R^{19} are independently selected from t-butyl, ethyl and benzyl and said groups are removed by treatment with trifluoroacetic acid, aqueous alkali or catalytic hydrogenation respectively, to yield the compound of formula (I) wherein R and R^4 (if present) are both H.

16. A process according to claim 13 or claim 14 wherein A is $(CH_2)_4$ and R^1 and R^2 are H to give a compound having the formula



(II)

wherein R, R^3 and R^5 are as previously defined for formula (I).

17. A process as claimed in claim 13 or claim 14 wherein R is H, R^3 is CO_2R^4 and R^4 is H.

18. A process as claimed in claim 13 wherein R^5 is methylene substituted by a group of the formula $-NHCOCR^{12}R^{13}R^{14}$, and R^{12} is NH_2, $R^{11}CONH-$ or $R^{11}SO_2NH-$, R^{13} is H and R^{14} is $-(CH_2)_4NH_2$.

7. A process as claimed in claim 1 wherein R^5 is C_1-C_6 alkyl, C_1-C_6 alkyl substituted by C_1-C_6 alkoxy or C_1-C_6 alkyl substituted by phenyl.

19. A process according to claim 13 wherein said compound of formula (I) produced is-:

2-{1-[2(S)-carboxy-3-(S-lysylamino)propyl]cyclopentyl-carbonylamino}-2,3-dihydroindene-2-carboxylic acid,

2-{1-[2(S)-carboxy-3-(N^2-methanesulphonyl-S-lysylamino)-propyl]cyclopentylcarbonylamino}-2,3-dihydroindene-2-carboxylic acid, or

2-{1-[2(S)-carboxy-3-(N^2-methanesulphonyl-S-lysylamino)-propyl]cyclopentylcarbonylamino}-2-hydroxymethyl-2,3-dihydroindene; or a biolabile ester derivatives thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 90/02156

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 C 237/24, A 61 K 31/16, C 07 C 233/63, 233/60, 235/40, 311/06, A 61 K 31/18

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 C 237/00, 235/00, 233/00, 311/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	GB, A, 2218983 (PFIZER) 29 November 1989 see examples; claims ---	1-19
A	EP, A, 0342850 (PFIZER) 23 November 1989 see examples; claims cited in the application ---	1-19
A	EP, A, 0343911 (PFIZER) 29 November 1989 see examples; claims cited in the application ---	1-19
A	EP, A, 0274234 (PFIZER) 13 July 1988 see examples; claims cited in the application ----------	1-19

[10] Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16th April 1991	29. 05. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	miss T. MORTENSEN

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ....., because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim numbers ..**.., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

** Claims searched incompletely: 1,2

The definition "biolabile ester-forming group" is obscure.

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9002156 SA 42884

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/05/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A- 2218983	29-11-89	None		
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